1,3-Dioxolanylpurine Nucleosides (2R,4R) and (2R,4S) with Selective Anti-HIV-1 Activity in Human Lymphocytes

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In order to study the structure–activity relationships of dioxolane nucleosides as potential anti-HIV-1 agents, various enantiomers of pure dioxolanylpurine nucleosides were synthesized and evaluated against HIV-1 in human peripheral blood mononuclear cells. The enantiomerically pure key intermediate 1, which was synthesized in nine steps from 1,6-anhydro-β-D-mannose, was condensed with 6-chloropurine, 6-chloro-2-fluoropurine, and 2,6-dichloropurine in the presence of TMS triflate. The chloro or fluoro substituents were readily converted into amino, *N*-methylamino, hydroxy, methoxy, thiol, and methylthio under appropriate reaction conditions. Upon evaluation of these dioxolanes, the guanine derivative **24** exhibited the most potent anti-HIV-1 activity without cytotoxicity up to 100 μM in various cells. The decreasing antiviral activity order of β-isomers was as follows: guanine > 6-chloro-2-aminopurine > 2-fluoroadenine ≥ adenine ≥ 2,6-diaminopurine > hypoxanthine > 2-chloroadenine > 6-chloropurine ≃ N^6-methyladenine ≃ 6-mercaptopurine ≃ 6-(methylthio)purine.

Introduction

Since the discovery of AZT[1] in 1985, a number of nucleosides have been identified as potent and promising anti-HIV agents.[2] AZT,[3] DDI,[4] and DDC[5] have been approved for the treatment of AIDS and AIDS-related complex, and several other nucleosides are undergoing clinical or preclinical development. Although AZT, DDI, and DDC have been reported to be clinically useful to treat AIDS either alone or in combination, side effects, toxicities, and drug resistance may limit their usefulness.[6] In order to discover more potent and less toxic compounds, a number of nucleosides were synthesized and evaluated against HIV in vitro. Among these, dioxolane[7,8] and oxathiolane[9] nucleosides are unique in that the classical carbohydrate moieties of nucleosides are replaced with dioxolane and oxathiolane ring systems. It is noteworthy that two of the oxathiolane nucleosides, (−)-(2*R*,5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (3TC)[9] and (−)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiacytidine (FTC) are undergoing advanced preclinical evaluations as anti-HIV agents. As a part of our efforts to discover useful anti-HIV nucleosides, we have recently reported the asymmetric syntheses of (+)-(2*S*,5*R*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine [D-like nucleoside][10] and (−)-(2*R*-5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine [L-like nucleoside][11] (3TC) (Figure 1) from chiral carbohydrate templates, 1,6-anhydrohexoses, and evaluated these compounds against HIV and human hepatitis B virus. It was found that 3TC is significantly more potent than (+)-(2*S*,5*R*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine. Interestingly, this is the first example of an L-nucleoside being more potent than a D-nucleoside. Furthermore, 3TC has been shown to be significantly less toxic than (+)-(2*S*,5*R*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine in CEM cells.[11]

Recently, we have reported an asymmetric synthesis of (−)-dioxolan-4-ylthymine from 1,6-anhydro-D-mannose and it was found to be a potent anti-HIV agent (EC_{50} = 0.39 μM) in human peripheral blood mononuclear (PBM) cells.[12] Interestingly, we have found that (±)-dioxolan-4-ylthymine was somewhat more potent than the enantiomerically pure (−)-D-isomer. Thus, synthesis of the antipode,[13a] the (+)-L-isomer, is of interest, which is in progress in our laboratory.

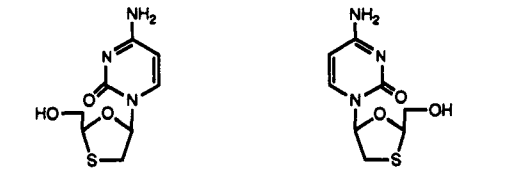

Figure 1.

Recently, we have reported the structure–activity relationships of enantiomerically pure dioxolanylpyrimidine nucleosides as anti-HIV agents in PBM cells.[13b] It was discovered that the unsubstituted cytosine derivative was the most potent compound (EC_{50} = 0.016 μM) although it exhibited marked toxicity. The uracil and 5-methylcytosine derivatives were inactive and 5-chloro and 5-bromo derivatives were moderately active. In this paper, the synthesis and structure–activity relationships of dioxolanylpurine nucleosides are reported.

Synthesis

The chiral key intermediate 1 was synthesized in nine steps from 1,6-anhydro-D-mannose,[12,13] which was condensed with silylated 6-chloropurine in the presence of TMSOTf to obtain the α,β-mixture of **3** and **2** (Scheme I). It is interesting to mention that initially formed N_3-isomers were converted to the desired N_9-isomers on heating of the reaction mixture.[14] The resulting anomeric mixture (1:1) was separated by flash silica gel column chromatography using hexanes–ethyl acetate (1:1) as the eluent. The 6-chloropurine derivative **2** was treated with ammonia in DME[15] and 2-mercaptoethanol/sodium methoxide in methanol[16] to give 6-amino **13** and 6-hydroxy **10** derivatives, respectively. Upon treatment of **13** and **10** with

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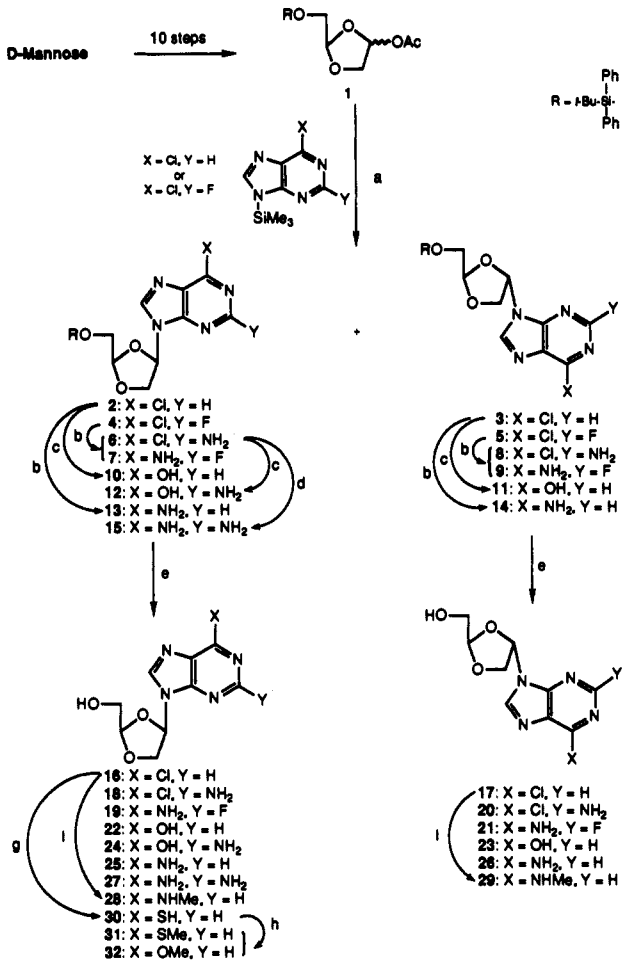
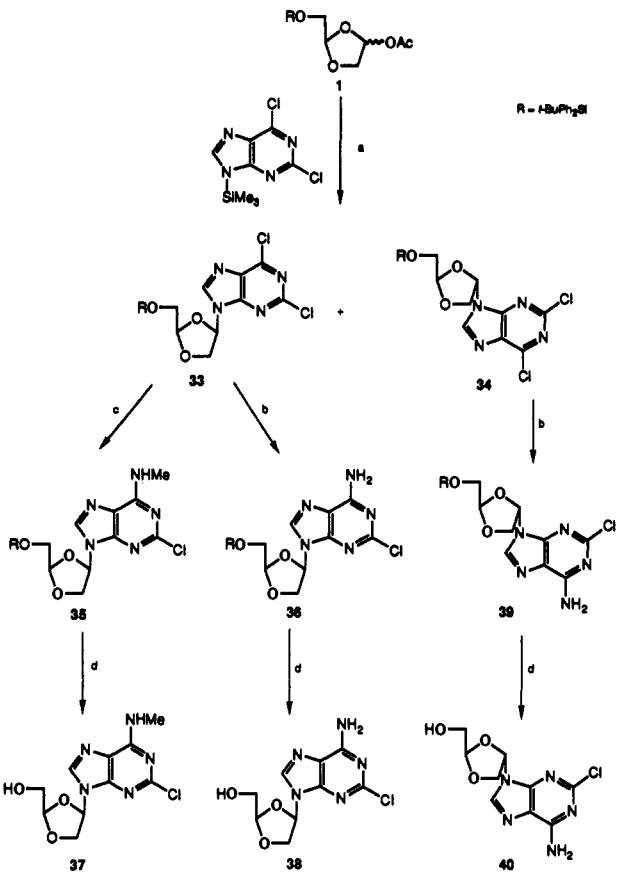
Scheme I[a]



[a] Reagents: (a) TMSOTf, CH_2Cl_2; (b) NH_3/DME; (c) $HSCH_2CH_2OH$, NaOMe, MeOH; (d) NH_3, EtOH; (e) n-Bu_4NF, THF; (f) $MeNH_2$, MeOH; (g) NaSH, MeOH; (h) MeI, NaOMe, MeOH.

Scheme II[a]



[a] Reagents; (a) TMSOTf, $ClCH_2CH_2Cl$; (b) NH_3, DME; (c) NH_2CH_3, CH_3OH; (d) n-Bu_4NF, THF.

n-Bu_4NF the desired nucleosides **25** and **22** were obtained in good yields. Treatment of **2** with n-Bu_4NF gave the 6-chloro derivative **16** which was converted to N^6-methyl derivative **28** upon treatment with $MeNH_2$ in a steel bomb at 85 °C. The 6-SH derivative **30** was obtained by the treatment of **16** with NaSH in methanol.[17] The reaction of **30** with CH_3I and NaOMe in methanol gave the S^6-methyl derivative **31** as well as the 6-OMe derivative **32**, which were separated by silica gel column chromatography. The corresponding α-isomers **11**, **14**, **17**, **23**, **26**, and **29** were obtained by the similar reactions as described for the β-isomers. 2,6-Disubstituted purine derivatives **18–21**, **24**, and **27** were synthesized by the condensation of acetate **1** with the silylated 6-chloro-2-fluoropurine, which gave a mixture of (α/β = 1/1.3) of **5** and **4** (Scheme I). Once again the initially formed N_3-isomers were converted into the desired N_9-isomers during stirring overnight at room temperature. The analytical sample was obtained from the separation of the α,β-mixture to the individual isomers **5** and **4** by preparative TLC using CH_2Cl_2-acetone (19:1) as the developing solvents. However, for the purpose of preparing the final products **18–21**, the mixture of **4** and **5** was treated with NH_3 in DME[15] to give a mixture of **6–9**, which was separated to the individual isomers **6** (24%), **7** (18.6%), **8** (25.8%), and **9** (16%). The guanine **12** and 2,6-diamino **15** derivatives were prepared by the treatment of **6** with 2-mercaptoethanol/NaOMe[16] and ammonia in ethanol,[18] respectively. The free nucleosides **18–21**, **24**, and **27** were obtained upon treatment of the corresponding 5′-silylated nucleosides with n-Bu_4NF in good yields. The α-isomers **20** and **21** were also prepared by the similar procedure as the β-isomers. Since N^6-methyl[17] and 2-chloroadenine nucleosides[19] are biologically of interest, compounds **37–40** were prepared from the condensation of acetate **1** with the silylated 2,6-dichloropurine followed by silica gel separation of the mixture of **33** and **34** and the treatment with $MeNH_2$ or ammonia[15] to give **35** and **36**, respectively (Scheme II). Desilylation of **35** and **36** afforded the desired nucleosides **37** and **38**. The physical and optical data and ^1H NMR spectral data of synthesized nucleotides are shown in Table I and Table II, respectively. The stability of (−)-(2R,4R)-dioxolan-4-ylguanine **24** and (−)-(2R,4R)-dioxolan-4-ylthymine[13] was tested in pH 2, 7, and 11 buffer solutions at 37 °C for 2 days. These two compounds were found to be stable under these conditions.

Anti-HIV-1 Activity

Anti-viral activities of the synthesized dioxolanyl nucleosides were evaluated in human PBM cells infected with HIV-1 strain LAV.[20] As shown in Table III, most of the compounds exhibited good to excellent anti-HIV activities. In general, the β-isomers were more potent than the α-isomers. The decreasing order of antiviral activity of the most potent compounds was as following: guanine > 6-Cl-2-NH_2-purine > 2-F-adenine ≥ adenine ≥ 2,6-diaminopurine ≥ hypoxanthine > 2-Cl-adenine > 6-Cl-purine ≃ N^6-Me-adenine ≃ 6-SH-purine ≃ 6-SMe-purine. It is interesting to note that the (+)-α-isomer of 6-Cl-purine derivatives **17** was found to be more potent than that of the corresponding (−)-β-isomer. This may be related to the greater overall cell toxicity of the compound compared to the β-isomer **16** which produced a low

Table I. Physical and Optical Data

no.	mp, °C (solvent)[a]	$[\alpha]^{25}_D$ deg	formula	anal.
2	128–129 (b)	−8.12 (c 1.09, MeOH)	$C_{25}H_{27}ClN_4O_3Si$	C, H, N
3	102–105 (b)	+16.49 (c 1.09, MeOH)	$C_{25}H_{27}ClN_4O_3Si·0.32(C_2H_5)_2O$	C, H, N
4 and 5	146–147		$C_{25}H_{26}ClFN_4O_3Si$	C, H, Cl, F, N
6	64–65	−38.39 (c 0.46, $CHCl_3$)	$C_{25}H_{28}ClN_5O_3Si$	C, H, Cl, N
7	181–182 (j)	−4.2 (c 0.25, $CHCl_3$)	$C_{25}H_{28}FN_5O_3Si$	C, H, F, N
8	60–61	+24.90 (c 0.25, $CHCl_3$)	$C_{25}H_{28}ClN_5O_3Si$	C, H, Cl, N
9	178–179 (j)	+30.2 (c 0.25, $CHCl_3$)	$C_{25}H_{28}FN_5O_3Si$	C, H, F, N
10	99–101 (e)	−1.10 (c 1.14, MeOH)	$C_{25}H_{28}N_4O_4Si·0.3MeOH$	C, H, N
11	152–154 (f)	+17.31 (c 1.08, MeOH)	$C_{25}H_{28}N_4O_4Si·0.37MeOH$	C, H, N
13	144–146 (f)	−1.84 (c 1.01, MeOH)	$C_{25}H_{29}N_5O_3Si$	C, H, N
14	122–123 (h)	+23.12 (c 1.01, MeOH)	$C_{25}H_{29}N_5O_3Si$	C, H, N
16	148–149 (c)	−29.09 (c 0.9, MeOH)	$C_9H_9ClN_4O_3·0.05C_6H_{14}$	C, H, N
17	113–116 (e)	+31.93 (c 0.86, MeOH)	$C_9H_9ClN_4O_3·0.05C_6H_{14}$	C, H, N
18	193 (j)	−50.25 (c 0.25, MeOH)	$C_9H_{10}ClN_5O_3$	C, H, Cl, N
19	247 (j)	−17.0 (c 0.25, MeOH)	$C_9H_{10}FN_5O_3$	C, H, F, N
20	67–68 (j)	+24.90 (c 0.5, MeOH)	$C_9H_{10}ClN_5O_3$	C, H, Cl, N
21	263–264 (j)	+49.86 (c 0.21, H_2O)	$C_9H_{10}FN_5O_3$	C, H, F, N
22	205–208 (d)	−19.76 (c 0.43, MeOH)	$C_9H_{10}N_4O_4$	C, H, N
23	228–231 (d)	+37.65 (c 0.75, MeOH)	$C_9H_{10}N_4O_4$	C, H, N
24	280 (dec H_2O)	−110 (c 0.25, H_2O)	$C_9H_{11}N_5O_4$	C, H, N
25	162–165 (g)	−30.74 (c 0.85, MeOH)	$C_9H_{11}N_5O_3$	C, H, N
26	176–179 (i)	+38.79 (c 1.09, MeOH)	$C_9H_{11}N_5O_3$	C, H, N
27	236–237 (j)	−71.44 (c 0.25, MeOH)	$C_9H_{12}N_6O_3$	C, H, N
28	139–141 (d)	−27.04 (c 0.91, MeOH)	$C_{10}H_{13}N_5O_3$	C, H, N
29	foam	+36.82 (c 0.95, MeOH)	$C_{10}H_{13}N_5O_3$	C, H, N
30	204–205 dec	−39.77 (c 0.28, H_2O)	$C_9H_{10}N_4O_3S$	C, H, N
31	115–116 (f)	−36.39 (c 0.12, MeOH)	$C_{10}H_{12}N_4O_3S$	C, H, N
32	111–112 (f)	−26.98 (c 0.61, MeOH)	$C_{10}H_{12}N_4O_4$	C, H, N
33	186–187 (j)	−8.6 (c 0.25, $CHCl_3$)	$C_{25}H_{26}Cl_2N_4O_3Si$	C, H, Cl, N
34	98–99 (j)	+32.7 (c 0.25, $CHCl_3$)	$C_{25}H_{26}Cl_2N_4O_3Si$	C, H, Cl, N
35	170 (j)	−7.1 (c 0.25, $CHCl_3$)	$C_{26}H_{30}ClN_5O_3Si·0.06CHCl_3$	C, H, Cl, N
36	199–200 (k)	−3.2 (c 0.25, $CHCl_3$)	$C_{25}H_{28}ClN_5O_3Si$	C, H, Cl, N
37	149 dec	−33.31 (c 0.25, MeOH)	$C_{10}H_{12}ClN_5O_3$	C, H, Cl, N
38	222 dec	−24.3 (c 0.22, MeOH)	$C_9H_{10}ClN_5O_3$	C, H, Cl, N
39	184–185 (j)	+33.7 (c 0.25, $CHCl_3$)	$C_{25}H_{28}ClN_5O_3Si·MeOH·0.05CHCl_3$	C, H, Cl, N
40	197–198 (j)	+39.8 (c 0.23, MeOH)	$C_9H_{10}ClN_5O_3$	C, H, Cl, N

[a] Solvents. [b] Ether. [c] Hexane–$CHCl_3$. [d] $CHCl_3$–MeOH. [e] Ether–hexane. [f] Hexane. [g] CH_2Cl_2–MeOH. [h] EtOAc–hexane. [i] EtOAc. [j] MeOH. [k] EtOAc–CH_2Cl_2.

multiplicity of the virus. The antiviral results presented in Table III are the average values of at least three separate experiments using different donor cells. Furthermore, we are confident in assigning the structures of these compounds since 6-chloropurines **2** (β) and **3** (α) were subsequently used for further modifications to adenine and hypoxanthine analogues in which β-isomers, as expected, were found to be more potent than the α-isomers. In summary, among the compounds tested, the guanine analogue **24** was the most potent anti-HIV-1 nucleoside with a low toxicity in PBM and Vero cells. It is interesting that the guanine analogue was more potent than either the 2,6-diamino or 2-amino-6-chloro derivative. We hypothesize that these compounds are likely to be substrates for adenosine deaminase. The hydrolysis at the 6-position of 2-amino-6-chloropurine **18** and 2,6-diaminopurine **27** would produce a guanine analogue **24**. Biochemical studies to validate this hypothesis are underway. Furthermore, virological and biochemical studies with those compounds will define their usefulness as anti-HIV agent for the treatment of AIDS.

Experimental Section

Melting points were determined on a Mel-temp II, laboratory device and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX 90Q or Bruker 300 Fourier transform spectrometer for 90-MHz or 300-MHz ^1H NMR spectra, respectively, with Me_4Si as internal standard; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). UV spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane and methylene chloride were obtained by distillation from CaH_2 prior to use.

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-6-chloropurine (2) and (+)-(2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-6-chloropurine (3). A mixture of 6-chloropurine (3.6 g, 23 mmol) and ammonium sulfate (catalytic amount) in hexamethyldisilazane (50 mL) was refluxed for 2 h under N_2. The clear solution obtained was concentrated in vacuo and the residue was dissolved in dry CH_2Cl_2 (20 mL) followed by a solution of acetate **1** (4.68 g, 12 mmol) in dry CH_2Cl_2 (30 mL) and TMSOTf (2.6 mL, 13 mmol) at room temperature. After stirring the reaction mixture for 30 min at room temperature, it was refluxed for 14 h under N_2. During reflux, the initially formed N_3-isomers were converted to desired N_9-condensed products.[14] The reaction solution was then poured into an ice-cold mixture of CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (20 mL), stirred for 15 min, and filtered through a Celite pad. The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was separated by silica gel column chromatography to give **2** [R_f = 0.64 (hexanes–EtOAc, 1:1), 1.62 g, 28%] and **3** (R_f = 0.71, 1.61 g, 28%) as syrups, which were crystallized from ether. **2**: UV (MeOH) λ_{max} 264.0 nm. **3**: UV (MeOH) λ_{max} 264.0 nm.

(2*R*,4*R*) and (2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-6-chloro-2-fluoropurine (4 and 5). A mixture of 2-fluoro-6-chloropurine (4.05 g, 23.47 mmol) and ammonium sulfate (catalytic amount) in hexamethyldisilazane (40 mL) was refluxed for 2 h. The resulting solution was concentrated under anhydrous conditions to yield silylated 2-fluoro-6-chloropurine as a white solid. To a cooled (0 °C) and stirred solution of silylated 2-fluoro-6-chloropurine (5.69 g, 23.69 mmol) and **1** (7.84 g, 19.57 mmol) in dry methylene chloride (175

mL) was added TMSOTf (4.41 mL, 23.44 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h, during which time, all the initially formed N_9-isomers were converted into desired N_9-isomers. The reaction mixture was quenched with saturated $NaHCO_3$ solution (50 mL), stirred for additional 20 min at room temperature, and evaporated to dryness under reduced pressure, and the residue was dissolved in EtOAc (200 mL), washed with water and brine, dried (anhydrous Na_2SO_4), filtered, and evaporated to give a solid residue, which was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford a mixture of β-anomer 4 and α-anomer 5 (1.3:1; β/α) as a white crystalline solid (6.30 g, 62.8%). The analytical sample was purified by preparative TLC using CH_2Cl_2–acetone (19:1) as the developing system to give 4 (R_f = 0.50) and 5 (R_f = 0.55) for NMR characterization: UV (MeOH) λ_{max} 269.0 nm.

(−)-(2*R*,4*R*)-2-Amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-6-chloropurine (6), (−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-fluoroadenine (7), (+)-(2*R*,4*S*)-2-Amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-6-chloropurine (8) and (+)-(2*R*,4*S*)-9[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-fluoroadenine (9). Dry ammonia gas was bubbled into a stirred solution of 4 and 5 (6.25 g, 12.18 mmol) in DME (125 mL) overnight. The solvent was evaporated under reduced pressure, and the residue was subjected to chromatographic separation of the four compounds on silica gel column (20–30% EtOAc in CH_2Cl_2). **6** (R_f = 0.35, 1.49 g, 24%): a white crystalline solid, UV (MeOH) λ_{max} 309.5 nm. **7** (R_f = 0.21, 1.12 g, 18.6%): colorless needles, UV (MeOH) λ_{max} 261.0, 268.0 (sh) nm. **8** (R_f = 0.43, 1.60 g, 25.76%): a white crystalline solid, UV (MeOH) λ_{max} 310.0 nm. **9** (R_f = 0.12, 0.96 g, 16%): a microcrystalline solid. UV (MeOH) λ_{max} 261.0, 269.0 (sh) nm.

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]hypoxanthine (10). A mixture of **2** (260 mg, 0.53 mmol), 2-mercaptoethanol (0.147 mL, 2.1 mmol), and NaOMe (2.1 mmol, prepared by dissolving 48.3 mg of Na in MeOH) in MeOH (20 mL) was refluxed for 1.5 h under N_2. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was dissolved in $CHCl_3$ (100 mL) and washed with saturated $NaHCO_3$ solution (10 mL) and brine and dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 40:1) to give **10** (223 mg, 89%), which was crystallized from ether–hexanes: UV (MeOH) λ_{max} 249.0 nm.

(+)-(2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]hypoxanthine (11). A mixture of **3** (260 mg, 0.53 mmol), 2-mercaptoethanol (0.147 mL, 2.1 mmol), and NaOMe (2.1 mmol, prepared by dissolving 48.3 mg of Na in MeOH) in MeOH (20 mL) was refluxed for 1.5 h under N_2. After work-up similar to that of **10**, purification by silica gel column chromatography ($CHCl_3$–MeOH, 30:1) gave **11** (247 mg, 99%), which was crystallized from ether–hexanes: UV (MeOH) λ_{max} 249.0 nm.

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]adenine (13). A solution of **2** (258 mg, 0.52 mmol) in NH_3/DME (20 mL) was heated at 85 °C in a steel bomb for 24 h. After cooling, the solvent was removed under vacuum and the residual syrup was purified by column chromatography (silica gel 230–400 mesh) using $CHCl_3$–MeOH (20:1) as the eluent to give **13** as a white solid (184 mg, 74%): UV (MeOH) λ_{max} 260.0 nm.

(+)-(2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]adenine (14). A solution of **3** (200 mg, 0.4 mmol) in NH_3/DME (20 mL) was heated at 85 °C in a steel bomb for 24 h. After work-up similar to that of **13**, purification by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) gave **14** as a white solid (190 mg, 99%): UV (MeOH) λ_{max} 260.0 nm.

(−)-(2*R*,4*R*)-6-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (16). A solution of **2** (0.3 g, 0.6 mmol) in THF (20 mL) was desilylated with 1 M *n*-Bu_4NF/THF (0.9 mL, 0.9 mmol) by stirring for 1 h at room temperature. After evaporation of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using $CHCl_3$–MeOH (20:1) as the eluent to give pure **16** (0.12 g, 82%), which was crystallized from hexanes–$CHCl_3$: UV (H_2O) λ_{max} 264.0 nm (ϵ 9290) (pH 7), 263.5 (ϵ 9630) (pH 2), 263.3 (s (150) (pH 11).

(+)-(2*R*,4*S*)-6-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (17). A solution of **3** (0.3 g, 0.6 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF/THF (0.9 mL, 0.9 mmol). After evaporation of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using $CHCl_3$–MeOH (20:1) as the eluent to give pure **17** (0.13 g, 96%), which was crystallized from ether–hexanes: UV (H_2O) λ_{max} 264.0 nm (ϵ 9720) (pH 7), 264.0 (ϵ 11200) (pH 2), 263.8 (ϵ 10840) (pH 11).

(−)-(2*R*,4*R*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (18). A solution of **6** (0.46 g, 0.91 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF/THF (1.1 mL, 1.1 mmol) to give **18** (R_f = 0.50, 0.21 g, 84%) as a crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 307.0 nm (ϵ 8370) (pH 7), 307.5 (ϵ 8590) (pH 2), 307.0 (ϵ 8800) (pH 11).

(−)-(2*R*,4*R*)-2-Fluoro-9-[2-hydroxymethyl)-1,3-dioxolan-4-yl]adenine (19). A solution of **7** (0.56 g, 1.12 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF/THF (1.35 mL, 1.35 mmol) to furnish **19** (0.24 g, 85%) as a white crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 260.8 nm (ϵ 17010), 268.5 (sh) nm (ϵ 13510) (pH 7), 261.0 (ϵ 16390), 268.5 (sh) (ϵ 13300) (pH 2), 260.8 (ϵ 17320), 268.5 (sh) (ϵ 13200) (pH 11).

(+)-(2*R*,4*S*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (20). A solution of **8** (0.41 g, 0.81 mmol) in THF (15 mL) was treated with 1 M *n*-Bu_4NF/THF (0.96 mL, 0.96 mmol) to furnish **20** (0.20 g, 92.7%) as a crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 307.0 nm (ϵ 8370) (pH 7), 307.5 (ϵ 8590) (pH 2), 307.0 (ϵ 8800) (pH 11).

(+)-(2*R*,4*S*)-2-Fluoro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]adenine (21). A solution of **9** (0.13 g, 0.26 mmol) in THF (15 mL) was treated with 1 M *n*-Bu_4NF/THF (0.32 mL, 0.32 mmol) to give **21** (0.05 g, 75%) as a white crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 260.8 (ϵ 16390), 268.5 (sh) nm (ϵ 12890) (pH 7), 261.0 (ϵ 15570), 268.5 (sh) (ϵ 174200) (pH 2), 260.8 (ϵ 16700), 268.5 (sh) (ϵ 13200) (pH 11).

(−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]hypoxanthine (22). A solution of **10** (173 mg, 0.36 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF/THF (0.68 mL, 0.68 mmol). After evaporation of the solvnt, the residue was chromatographed over silica gel (230–400 mesh) using $CHCl_3$–MeOH (15:1) as the eluent to give pure **22** (70 mg, 81%) as a white solid: UV (H_2O) λ_{max} 247.9 nm (ϵ 12320 nm (ϵ 12320) (pH 7), 258.5 (ϵ 14350) (pH 2), 252.9 (ϵ 16630) (pH 11).

(+)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]hypoxanthine (23). A solution of **11** (180 mg, 0.38 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF/THF (0.70 mL, 0.70 mmol). After evaporation of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using $CHCl_3$–MeOH (20:1) as the eluent to give pure **23** (67 mg, 75%) as a white solid: UV (H_2O) λ_{max} 248.4 nm (ϵ 13060) (pH 7), 248.5 (ϵ 13570) (pH 2), 253.4 (ϵ 13630) (pH 11).

(−)-(2*R*,4*R*)-9-(Hydroxymethyl)-1,3-dioxolan-4-yl]guanine (24). A mixture of **6** (0.29 g, 0.57 mmol), $HSCH_2CH_2OH$ (0.51 mL), and 1 M NaOMe/MeOH (11.5 mL) in MeOH (20 mL) was refluxed for 3 h. The reaction mixture was cooled and neutralized with glacial AcOH. The solution was evaporated to dryness, then the residue was triturated with $CHCl_3$, and filtered, and the filtrate was taken to dryness to give crude compound **12** (0.21 g, 75%), which without further purification was subjected to desilylation according to the same procedure described for **20** to give compound **24** (0.07 g, 61%) as a micro crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 252.0 (ϵ 12800), 274.0 (sh) nm (ϵ 8730) (pH 7), 254.4 (ϵ 12130), 277.5 (sH) (ϵ 8070) (pH 2), 264.3 (ϵ 10.800) (pH 11).

(−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]adenine (25). A solution of **13** (130 mg, 0.27 mmol) in THF (10 mL) was treated with 1 M *n*-Bu_4NF/THF (0.3 mL, 0.3 mmol). After evaporation of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using CH_2Cl_2–MeOH (15:1) as the eluent to give pure **25** (53 mg, 82%) as a white solid: UV (H_2O) λ_{max} 258.9 nm (ϵ 15240) (pH 7), 257.0 (ϵ 15340) (pH 2), 258.9 (ϵ 14990) (pH 11).

(+)-(2*R*,4*S*)-9-[2-Hydroxymethyl)-1,3-dioxolan-4-yl]adenine (26). A solution of **14** (140 mg, 0.29 mmol) in THF (10 mL)

Table II. ^{1}H NMR Data

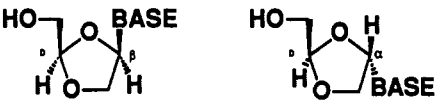
no.	H-1[d]	H_a-2′	H_b-2′	H-4′	H-5′ (a and b)	other signals
2	6.55 (dd, $J_{1',2'a}$ = 5.1 $J_{1',2'b}$ = 1.5)	4.50 (dd, $J_{2'a,2'b}$ = 10.1, $J_{2'a,1'}$ = 1.5)	4.30 (dd, $J_{2'b,2'a}$ = 10.1, $J_{2'b,1'}$ = 5.1)	5.23 (t, $J_{4',5'}$ = 3.5)	3.91 (d, $J_{5',4'}$ = 3.5)	1.07 (s, *t*-Bu), 7.51 (m, Ar), 8.37 (s, H-8), 8.72 (s, H-2)[b]
3	6.57 (dd, $J_{1',2'a}$ = 4.6, $J_{1',2'b}$ = 3.0)	4.50 (m)	5.65 (t, $J_{4',5'}$ = 3.1)	3.80 (d, $J_{5',4'}$ = 3.1)		1.09 (s, *t*-Bu), 7.55 (m, Ar), 8.29 (s, H-8), 8.76 (s, H-2)[b]
4	6.45 (d, $J_{1',2'b}$ = 6.0)	4.48 (d, $J_{2'a,2'b}$ = 9.0)	4.30 (dd, $J_{2'b,2'a}$ = 9.0, $J_{2'b,1'}$ = 6.0)	5.21 (t, $J_{4',5'}$ = 3.0)	3.93 (dd, $J_{5'b,5'a}$ = 10.5, $J_{5'a,4'}$ = 3.0), 3.89 (dd, $J_{5'b,5'a}$ = 10.5, $J_{5'b,4'}$ = 3.0)	1.07 (s, *t*-Bu), 7.32–7.67 (m, Ar), 8.38 (s, H-8)[b]
5	6.47 (dd, $J_{1',2'a}$ = 6.0, $J_{1',2'b}$ = 3.0)	4.51 (dd, $J_{2'a,2'b}$ = 9.0, $J_{2'a,1'}$ = 6.0)	4.41 (dd, $J_{2'b,2'a}$ = 9.0, $J_{2'b,1'}$ = 3.0)	5.64 (t, $J_{4',5'}$ = 3.0)	3.82 (dd, $J_{5'b,5'a}$ = 12.0, $J_{5'a,4'}$ = 3.0), 3.76 (dd, $J_{5'b,5'a}$ = 12.0, $J_{5'b,4'}$ = 3.0)	1.08 (s, *t*-Bu), 7.37–7.72 (m, Ar), 8.25 (s, H-8)[b]
6	6.30 (d, $J_{1',2'}$ = 2.7)	4.46 (d, $J_{2'a,2'b}$ = 12.2)	4.23 (dd, $J_{2'b,2'a}$ = 12.2, $J_{2'b,1'}$ = 3.8)	5.21 (t, $J_{4',5'}$ = 3.0)	3.91 (dd, $J_{5'a,5'b}$ = 10.0, $J_{5'a,4'}$ = 3.0), 3.83 (dd, $J_{5'b,5'a}$ = 10.0, $J_{5'b,4'}$ = 3.0)	1.06 (s, *t*-Bu), 5.20 (br s, NH_2), 7.33–7.67 (m, Ar), 7.96 (s, H-8)[b]
7	6.39 (d, $J_{1',2'}$ = 4.0)	4.40 (d, $J_{2'a,2'b}$ = 9.9)	4.24 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 3.0)	5.17 (t, $J_{4',5'}$ = 3.0)	3.92 (dd, $J_{5'a,5'b}$ = 9.8, $J_{5'a,4'}$ = 3.0), 3.85 (dd, $J_{5'b,5'a}$ = 9.8, $J_{5'b,4'}$ = 3.0)	1.07 (s, *t*-Bu), 6.10 (br s, NH_2), 7.35–7.69 (m, Ar), 8.05 (s, H-8)[b]
8	6.35 (t, $J_{1',2'}$ = 3.3)	4.47 (dd, $J_{2'a,2'b}$ = 12.0, $J_{2'a,1'}$ = 3.0)	4.40 (dd, $J_{2'b,2'a}$ = 12.0, $J_{2'b,1'}$ = 3.0)	5.58 (t, $J_{4',5'}$ = 2.7)	3.70 (dd, $J_{5'a,5'b}$ = 12.2, $J_{5'a,4'}$ = 2.7), 3.73 (dd, $J_{5'b,5'a}$ = 12.2, $J_{5'b,4'}$ = 2.7)	1.08 (s, *t*-Bu), 5.18 (br s, NH_2), 7.40–7.72 (m, Ar), 7.93 (s, H-8)[b]
9	6.42 (d, $J_{1',2'}$ = 4.0)	4.46 (dd, $J_{2'a,2'b}$ = 10.0, $J_{2'a,1'}$ = 4.4)	4.38 (dd, $J_{2'b,2'a}$ = 10.0, $J_{2'b,1'}$ = 2.2)	5.61 (t, $J_{4',5'}$ = 2.2)	3.78 (dd, $J_{5'a,5'b}$ = 11.0, $J_{5'a,4'}$ = 2.2), 3.74 (dd, $J_{5'b,5'a}$ = 11.0, $J_{5'b,4'}$ = 2.2)	1.08 (s, *t*-Bu), 5.18 (br s, NH_2), 7.40–7.72 (m, Ar), 7.93 (s, H-8)[b]
10	6.42 (dd, $J_{1',2'a}$ = 3.3, $J_{1',2'b}$ = 1.3)	4.45 (dd, $J_{2'a,2'b}$ = 9.8, $J_{2'a,1'}$ = 1.3)	4.25 (dd, $J_{2'b,2'a}$ = 9.8, $J_{2'b,1'}$ = 3.3)	5.21 (t, $J_{4',5'}$ = 3.5)	3.89 (d, $J_{5',4'}$ = 3.5)	1.07 (s, *t*-Bu), 1.70 (br s, 6-OH), 7.54 (m, Ar), 8.05 (s, H-8), 8.24 (s, H-2)[b]
11	6.46 (dd, $J_{1',2'b}$ = 4.5, $J_{1',2'a}$ = 2.8)	4.47 (d, $J_{2'a,1'}$ = 4.5)	4.29 (d, $J_{2'b,1'}$ = 2.8)	5.62 (t, $J_{4',5'}$ = 3.9)	3.79 (d, $J_{5',4'}$ = 3.1)	1.09 (s, *t*-Bu), 1.76 (br s, 6-OH), 7.55 (m, Ar), 8.00 (s, H-8), 8.21 (s, H-2)[b]
13	6.48 (dd, $J_{1',2'a}$ = 5.0, $J_{1',2'b}$ = 1.7)	4.46 (dd, $J_{2'a,2'b}$ = 9.8, $J_{2'a,1'}$ = 1.7)	4.25 (dd, $J_{2'b,2'a}$ = 9.8, $J_{2'b,1'}$ = 5.0)	5.21 (t, $J_{4',5'}$ = 3.5)	3.91 (d, $J_{5',4'}$ = 3.5)	1.07 (s, *t*-Bu), 5.69 (br s, NH_2), 7.51 (m, Ar), 8.37 (s, H-8), 8.72 (s, H-2)[b]
14	6.50 (dd, $J_{1',2'a}$ = 4.2, $J_{1'3,2'b}$ = 3.0)	4.47 (d, $J_{2'a,1'}$ = 3.0)	4.46 (d, $J_{2'b,1'}$ = 4.2)	5.62 (t, $J_{4',5'}$ = 3.1)	3.78 (d, $J_{5',4'}$ = 3.1)	1.08 (s, *t*-Bu), 5.69 (br s, NH_2), 7.55 (m, Ar), 7.97 (s, H-8), 8.37 (s, H-2)[b]
16	6.58 (d, $J_{1',2'a}$ = 5.0)	4.65 (dd, $J_{2'a,2'b}$ = 10.1)	4.27 (dd, $J_{2'b,2'a}$ = 10.1, $J_{2'b,1'}$ = 5.0)	5.12 (t, $J_{4',5'}$ = 2.6)	3.65 (dd, $J_{5',OH}$ = 5.5, $J_{5',4'}$ = 2.6)	5.13 (t, $J_{OH,5'}$ = 5.5, OH), 8.81 (s, H-8), 8.84 (s, H-2)[a]
17	6.60 (t, $J_{1',2'}$ = 5.0)	4.50 (m)		5.58 (t, $J_{4',5'}$ = 3.6)	3.52 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.6)	5.04 (t, $J_{OH,5'}$ = 6.0, OH), 8.83 (s, H-8, H-2)[a]
18	6.29 (d, $J_{1',2'}$ = 4.8)	4.54 (d, $J_{2'a,2'b}$ = 9.9)	4.19 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 5.1)	5.06 (t, $J_{4',5'}$ = 2.9)	3.60 (m)	5.13 (t, $J_{OH,5'}$ = 6.1, OH), 6.92 (br s, NH_2), 8.08 (s, H-8)[a]
19	6.30 (d, $J_{1',2'}$ = 5.0)	4.52 (d, $J_{2'a,2'b}$ = 10.0)	4.20 (dd, $J_{2'b,2'a}$ = 10.0, $J_{2'b,1'}$ = 5.0)	5.05 (t, $J_{4',5'}$ = 2.5)	3.61 (dd, $J_{5',OH}$ = 5.0, $J_{5',4'}$ = 2.5)	5.15 (t, $J_{OH,5'}$ = 5.0, OH), 7.87 (br s, NH_2), 8.27 (s, H-8)[a]
20	6.31 (dd, $J_{1',2'a}$ = 5.5, $J_{1',2'b}$ = 5.0)	4.36–4.48 (m)		5.49 (t, $J_{4',5'}$ = 5.0)	3.46–3.51 (m)	5.05 (t, $J_{OH,5'}$ = 5.0, OH), 7.04 (br s, NH_2), 8.28 (s, H-8)[a]
21	6.33 (t, $J_{1',2'}$ = 4.8)	4.40 (d, $J_{2',1'}$ = 4.8)		5.45 (t, $J_{4',5'}$ = 3.5)	3.38–3.66 (m)	4.98 (t, $J_{OH,5'}$ = 6.2, OH), 7.83 (br s, NH_2), 8.24 (s, H-8)[a]
22	6.38 (dd, $J_{1',2'a}$ = 5.3, $J_{1',2'b}$ = 1.1)	4.52 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.1)	4.35 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 5.3)	5.07 (t, $J_{4',5'}$ = 3.1)	3.62 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.1)	5.12 (t, $J_{OH,5'}$ = 6.0, OH), 7.0 (br s, 6-OH), 8.07 (s, H-8), 8.24 (s, H-2)[a]
23	6.43 (t, $J_{1',2'}$ = 4.8)	4.44 (d, $J_{2',1'}$ = 4.8)		5.49 (t, $J_{4',5'}$ = 3.7)	3.50 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.7)	2.35 (br s, 6-OH), 5.01 (t, $J_{OH,5'}$ = 6.0, OH), 8.08 (s, H-8), 8.24 (s, H-2)[a]
24	6.13 (dd, $J_{1',2'a}$ = 1.8, $J_{1',2'b}$ = 5.0)	4.43 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.8)	4.15 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 5.0)	4.99 (t, $J_{4',5'}$ = 3.2)	3.57 (dd, $J_{5',5'OH}$ = 5.6, $J_{5',4'}$ = 3.2)	5.07 (t, $J_{OH,5'}$ = 5.6, OH), 6.45 (br s, NH_2), 7.82 (s, H-8), 10.57 (br s, OH)[a]
25	6.42 (dd, $J_{1',2'a}$ = 4.4)	4.53 (d, $J_{2'a,2'b}$ = 9.8)	4.23 (dd, $J_{2'b,2'a}$ = 9.5, $J_{2'b,1'}$ = 4.4)	5.07 (t, $J_{4',5'}$ = 3.1)	3.62 (dd, $J_{5',OH}$ = 5.7, $J_{5',4'}$ = 3.1)	5.14 (t, $J_{OH,5'}$ = 5.7, OH), 7.26 (br s, NH_2), 8.16 (s, H-8), 8.28 (s, H-2)[a]
26	6.44 (dd, $J_{1',2'a}$ = 5.3, $J_{1',2'a}$ = 4.4)	4.43 (m)		5.55 (t, $J_{4',5'}$ = 3.7)	3.50 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.7)	4.99 (t, $J_{OH,5'}$ = 6.0, OH), 7.29 (br s, NH_2), 8.17 (s, H-8), 8.29 (s, H-2)[a]
27	6.19 (dd, $J_{1',2'a}$ = 1.8, $J_{1',2'b}$ = 5.7)	4.43 (dd, $J_{2'a,2'b}$ = 9.4, $J_{2'a,1'}$ = 1.8)	4.15 (dd, $J_{2'b,2'a}$ = 9.4, $J_{2'b,1'}$ = 5.7)	5.03 (t, $J_{4',5'}$ = 3.0)	3.59 (dd, $J_{5',5'OH}$ = 5.6, $J_{5',4'}$ = 3.0)	5.13 (t, $J_{OH,5'}$ = 6.3, OH), 5.78 (br s, NH_2), 6.68 (br s, NH_2), 8.27 (s, H-8)[a]
28	6.42 (dd, $J_{1',2'a}$ = 5.3, $J_{1',2'b}$ = 1.8)	4.52 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.8)	4.23 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'b,1'}$ = 5.3)	5.08 (t, $J_{4',5'}$ = 3.1)	3.62 (dd, $J_{5',OH}$ = 6.1, $J_{5',4'}$ = 3.1)	2.99 (d, $J_{NMe,NH}$ = 4.5, NMe), 5.14 (t, $J_{OH,5'}$ = 6.1, OH), 7.70 (d, $J_{NH,NMe}$ = 4.5), 8.23 (s, H-8), 8.27 (s, H-2)[a]
29	6.44 (pseudo t, $J_{1',2'b}$ = 5.3, $J_{1',2'a}$ = 4.4)	4.46 (d, $J_{2'a,1'}$ = 5.3)	4.17 (d, $J_{2'b,1'}$ = 4.4)	5.51 (t, $J_{4',5'}$ = 3.5)	3.49 (dd, $J_{5',OH}$ = 5.7), $J_{5',4'}$ = 3.5)	2.99 (d, $J_{NMe,NH}$ = 4.0, NMe), 4.99 (t, $J_{OH,5'}$ = 5.7, OH), 7.72 (d, $J_{NH,NMe}$ = 4.0), 8.24 (s, H-8), 8.27 (s, H-2)[a]
30	6.40 (d, $J_{1',2'a}$ = 5.3)	4.57 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.3)	4.23 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'b,1'}$ = 5.3)	5.08 (t, $J_{4',5'}$ = 2.9)	3.64 (dd, $J_{5',OH}$ = 6.4, $J_{5',4'}$ = 2.9)	5.11 (t, $J_{OH,5'}$ = 6.4, OH), 8.22 (s, H-8), 8.43 (s, H-2), 13.77 (br s, SH)[a]
31	6.59 (dd, $J_{1',2'a}$ = 5.0, $J_{1',2'a}$ = 1.5)	4.66 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.5)	4.34 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'a,1'}$ = 5.0)	5.06 (t, $J_{4',5'}$ = 2.4)	3.81 (d, $J_{5',4'}$ = 2.4)	2.69 (s, SMe), 8.56 (s, H-8), 8.66 (s, H-2)[c]
32	6.59 (dd, $J_{1',2'a}$ = 5.3, $J_{1',2'b}$ = 1.8)	4.63 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.8)	4.38 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'b,1'}$ = 5.3)	5.19 (t, $J_{4',5'}$ = 2.2)	3.82 (d, $J_{5',4'}$ = 2.2)	4.13 (s, OMe), 8.47 (s, H-8), 8.49 (s, H-2)[c]
33	6.49 (dd, $J_{1',2'b}$ = 4.7, $J_{1',2'a}$ = 1.3)	4.47 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.3)	4.26 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 4.7)	5.20 (t, $J_{4'}3,_{5'}$ = 3.1)	3.91 (d, $J_{5',4'}$ = 3.1)	1.07 (s, *t*-Bu), 7.65, 7.39 (m, Ar), 8.39 (s, H-8)[b]

Table II. (Continued)

no.	H-1[d]	H_a-2′	H_b-2′	H-4′	H-5′ (a and b)	other signals
34	6.51 (dd, $J_{1',2'}$ = 4.5, $J_{1',2'}$ = 2.34)	4.44 (m)		5.63 (t, $J_{4',5'}$ = 3.1)	3.79 (d, $J_{5',4'}$ = 3.1)	1.08 (s, *t*-Bu), 7.66, 7.43 (m, Ar), 8.25 (s, H-8)[b]
35	6.42 (dd, $J_{1',2'b}$ = 4.9, $J_{1',2'a}$ = 1.6)	4.38 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.6)	4.20 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'b,1'}$ = 4.9)	5.16 (t, $J_{4',5'}$ = 3.5)	3.89 (d, $J_{5',4'}$ = 3.5)	1.07 (s, *t*-Bu), 3.19 (d, $J_{NMe,NH}$ = 5.04, NMe), 5.96 (br s, NH), 7.66, 7.97 (m, Ar), 7.97 (s, H-8)[b]
36	6.43 (dd, $J_{1',2'b}$ = 4.8, $J_{1',2'a}$ = 1.4)	4.40 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.4)	4.22 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 4.8)	5.17 (t, $J_{4',5'}$ = 3.2)	3.91 (d, $J_{5',4'}$ = 3.2)	1.07 (s, *t*-Bu), 6.11 (br s, NH_2), 7.68, 7.38 (m, Ar), 8.06 (s, H-8)[b]
37	6.35 (dd, $J_{1',2'b}$ = 5.2, $J_{1',2'a}$ = 1.3)	4.52 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.3)	4.20 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 5.2)	5.06 (t, $J_{4',5'}$ = 2.9)	3.61 (dd, $J_{5',OH}$ = 5.9, $J_{5',4'}$ = 2.9)	2.92 (d, $J_{NMe,NH}$ = 4.0, NMe), 5.14 (t, $J_{OH,5'}$ = 5.9, OH), 8.19 (br s, NH), 8.29 (s, H-8)[a]
38	6.34 (dd, $J_{1',2'b}$ = 5.1, $J_{1',2'a}$ = 1.3)	4.52 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 1.3)	4.20 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 5.1)	5.04 (t, $J_{4',5'}$ = 2.9)	3.61 (dd, $J_{5',OH}$ = 5.9, $J_{5',4'}$ = 2.9)	5.08 (t, $J_{OH,5'}$ = 5.9, OH), 7.79 (br s, NH_2), 8.29 (s, H-8)[a]
39	6.46 (dd, $J_{1',2'}$ = 4.5, $J_{1',2'}$ = 2.5)	4.38 (m)		5.60 (t, $J_{4',5'}$ = 3.1)	3.76 (d, $J_{5',4'}$ = 3.1)	1.08 (s, *t*-Bu), 6.13 (br s, NH_2), 7.68, 7.39 (m, Ar), 7.94 (s, H-8)[b]
40	6.38 (t, $J_{1',2'}$ = 4.7)	4.42 (d, $J_{2',1'}$ = 4.7)		5.47 (t, $J_{4',5'}$ = 3.6)	3.49 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.6)	5.02 (t, $J_{OH,5'}$ = 6.0, OH), 7.83 (br s, NH_2), 8.31 (s, H-8)[a]

[a] DMSO-d_6. [b] $CDCl_3$. [c] CD_3COCD_3. [d] Part per million downfield from TMS. [e] In order to avoid complications, the furanose numbering system was used for interpretation of the NMR data.

Table III. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of (2*R*)-Dioxolanylpurine Nucleosides in PBM Cells and Cytotoxicity in Vero and CEM Cells



compd no.	base	anomer	anti-HIV-1[a] in PBM cells: EC_{50}, μM	cytotoxicity in PBM cells: IC_{50}, μM	cytotoxicity in Vero cells: IC_{50}, μM	cytotoxicity in CEM cells IC_{50}, μM
25	adenine	(−)-β	0.5	>100	>100	>100
26	adenine	(+)-α	6.2	>100	>100	>100
22	hypoxanthine	(−)-β	5.0	>100	>100	>100
23	hypoxanthine	(+)-α	>100	>100	>100	>100
16	6-Cl-purine	(−)-β	22.8	>100	>100	>100
17	6-Cl-purine	(+)-α	11.1	>100	>100	57.6
28	N^6-Me-adenine	(−)-β	14.3	>100	>100	>100
29	N^6-Me-adenine	(+)-α	30.3	>100	>100	>100
30	6-SH-purine	(−)-β	26.5	>100	>100	>100
31	6-SMe-purine	(−)-β	25.1	>100	>100	>100
32	6-OMe-purine	(−)-β	58.1	>100	>100	>100
18	6-Cl-2-NH_2-purine	(−)-β	0.09	>100	>100	>100
20	6-Cl-2-NH_2-purine	(+)-α	23.1	>100	>100	>100
19	2-F-adenine	(−)-β	0.3	>100	93.3	>100
21	2-F-adenine	(+)-α	2.5	>100	>100	>100
24	guanine	(−)-β	0.03	>100	>100	>100
27	2,6-diaminopurine	(−)-β	0.7	>100	>100	>100
37	2-Cl-N^6-Me-adenine	(−)-β	40.0	>100	>100	>100
38	2-Cl-adenine	(−)-β	1.7	>100	>100	>100
40	2-Cl-adenine	(+)-α	39.9	>100	>100	>100
	AZT		0.004	>100	28.0	30.9

[a] Mean of triplicate values.

was treated with 1 M *n*-Bu_4NF/THF (0.32 mL, 0.32 mmol). After evaporation of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using CH_2Cl_2–MeOH (20:1) as the eluent to give pure **26** (67 mg, 96%) as a white solid, which was triturated with ethyl acetate: UV (H_2O) λ_{max} 258.9 nm (ε 15800) (pH 7), 257.0 (ε 16020) (pH 2), 259.4 (ε 15070) (pH 11).

(−)-(2*R*,4*R*)-2-Amino-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]adenine (27). A steel bomb was charged with compound **6** (0.28 g, 0.55 mmol) and anhydrous EtOH (20 mL) saturated with NH_3 and heated at 90 °C for 6 h. After cooling, the compound **15** (0.26 g, 95%) obtained on evaporation of the solvent in vacuo was desilylated according to the same procedure described for preparation of **16** to give **27** (0.10 g, 75%) as white micro needles, recrystallized from MeOH: UV (H_2O) λ_{max} 279.0 nm (ε 8040) (pH 7), 290.0 (ε 7070) (pH 2), 278.8 (ε 7580) (pH 11).

(−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-N^6-methyladenine (28). A solution of **16** (50 mg, 0.22 mmol) and methylamine (40 wt.% solution in H_2O, 2 mL) in MeOH (10 mL) was heated at 85 °C in a steel bomb for 5 h. After cooling, the solvents were removed under vacuum. The residual syrup was purified by column chromatography (silica gel 230–400 mesh) using $CHCl_3$–MeOH (15:1) as the eluent to give **28** as a white solid (52 mg, 93%): UV (H_2O) λ_{max} 265.5 nm (ε 5100) (pH 7), 264.0 (ε 4150) (pH 2), 265.5 (ε 4600) (pH 11).

(+)-(2*R*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-N^6-methyladenine (29). A solution of **17** (67 mg, 0.3 mmol) and methylamine (40 wt.% solution in H_2O, 2.8 mL) in MeOH (10 mL) was heated at 85 °C in a steel bomb for 6 h. After workup similar to that of **28**, purification by silica gel column chromatography ($CHCl_3$–MeOH, 15:1) gave **29** as a colorless foam (57 mg, 76%): UV (H_2O) λ_{max} 265.3 nm (ε 18000) (pH 7), 261.9 (ε 18760) (pH 2), 265.3 (ε 17300) (pH 11).

(−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-6-mercaptopurine (30). A stream of H_2S was bubbled through a refluxing solution of **16** (0.18 g, 0.7 mmol) in anhydrous MeOH (30 mL) for 10 min. Then, NaSH in anhydrous MeOH (1 N, 2.1 mL) was added dropwise while heating and the introduction of H_2S was continued for 1.5 h. The yellowish solution was cooled to room temperature and the pH of the solution was adjusted to 6–7 with 1 N methanolic acetic acid. Solvents were removed under reduced pressure to give yellowish solid which was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to

yield **30** as a colorless solid (0.14 g, 76%): UV (H_2O) λ_{max} 320.0 nm (ϵ 20,300) (pH 7), 320.7 (ϵ 21,130) (pH 2), 309.2 (ϵ 20,880) (pH 11).

(−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-*S*^{6}-methyl-6-mercaptopurine (31) and (−)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-*O*^{6}-methylhypoxanthine (32). A solution of **30** (80 mg, 0.3 mmol) in MeOH (15 mL) containing NaOMe (0.3 mmol, prepared by dissolving 7.2 mg of Na in MeOH) was stirred with MeI (0.07 mL) for 1.5 h at room temperature. After removal of the solvent, the residual mixture was separated by column chromatography (silica gel 230–400 mesh) using $CHCl_3$–MeOH (20:1) as the eluent to give **31** (R_f = 0.54, 20 mg, 23.7%) and **32** (R_f = 0.50, 30 mg, 36%), which was crystallized from hexanes. **31**: UV (H_2O) λ_{max} 258.8 (sh) nm (ϵ 10890) (pH 7), 289.8 (sh) (ϵ 14410) (pH 2), 289.8 (sh) (ϵ 14130) (pH 11). **32**: UV (H_2O) λ_{max} 247.4 nm (ϵ 8100) (pH 7), 247.4 (ϵ 9100) (pH 2), 247.4 (ϵ 8150) (pH 11).

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2,6-dichloropurine (33) and (+)-(2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2,6-dichloropurine (34). A mixture of dichloropurine (3.06 g, 16.22 mmol) in dry dichloroethane (80 mL), hexamethyldisilazane (25 mL), and ammonium sulfate (catalytic amount) was refluxed for 3 h under N_2. The resulting clear solution was cooled to −10 °C. To this cooled silylated dichloropurine were added a solution of **1** (5.0 g, 12.48 mmol) in dry dichloroethane (50 mL) and TMSOTf (3.13 mL, 16.22 mmol) and the mixture was stirred for 10 min. The temperature was brought upto room temperature and the mixture was stirred overnight. TLC indicated the presence of N_3-isomer. The reaction mixture was refluxed for further 2 h at 80 °C (until almost all the N_3-isomer converted to N_9-isomer). After cooling the reaction mixture, saturated $NaHCO_3$ (40 mL) was added and the mixture was stirred for 15 min. The solvent was evaporated and the solid was dissolved in EtOAc and washed with water and brine, dried, filtered, and evaporated to give the crude product. This crude product was purified on a silica column (EtOAc–hexanes, 1:4) to yield pure α,β mixture of **34** and **33** [R_f = 0.57 (hexanes–EtOAc, 3:2), 4.30 g, 67%, α:β, 1:1.2]. Part of this α,β mixture was used in the next step without separation. The α,β isomers from the other part were separated by boiling the mixture in MeOH and filtering the solid after cooling. The solid product was found to be the pure β isomer. **33**: UV (MeOH) λ_{max} 272.5 nm. The filtrate on evaporation to dryness gave the α-isomer, **34**: UV (MeOH) λ_{max} 272.5 nm.

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-chloro-*N*^{6}-methyladenine (35). A solution of **33** (0.30 g, 0.56 mmol) in DME (30 mL) and methylamine (3 mL) was sealed in a steel bomb and heated at 80 °C for 5 h. After cooling the mixture, the solvent was evaporated and the crude product was boiled in MeOH, and filtered to give **35** (0.245 g, 82%) as a white solid: UV (MeOH) λ_{max} 270.0 nm.

(−)-(2*R*,4*R*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-chloroadenine (36) and (+)-(2*R*,4*S*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-chloroadenine (39). An α,β mixture of **34** and **33** (3.0 g, 5.66 mmol) in DME/NH_3 (50 mL, saturated at 0 °C) was sealed in a steel bomb and heated at 80 °C for 5 h. After cooling the mixture, the solvent was evaporated and the crude product was separated by silica gel column (EtOAc–CH_2Cl_2, 1:4) to yield **36** [R_f = 0.50 (45% EtOAc–CH_2Cl_2), 1.41 g, 48.9%] as a white solid and **39** [R_f = 0.45 (45% EtOAc–CH_2Cl_2), 1.18 g, 40.9%] as a foam (which was boiled in MeOH to give a white solid). **36**: UV (H_2O) λ_{max} 264.0 nm. **39**: UV (H_2O) λ_{max} 264.0 nm.

(−)-(2*R*,4*R*)-2-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]-*N*^{6}-methyladenine (37). A solution of **35** (0.26 g, 0.49 mmol) in THF (15 mL) was treated with 1 M *n*-Bu_4NF–THF (0.6 mL, 0.6 mmol). Evaporation of the solvent gave the crude product which was purified by silica gel chromatography (MeOH–$CHCl_3$, 1:20) to give **37** (0.135 g, 95.7%) as a white solid: UV (H_2O) λ_{max} 269.5 nm (ϵ 17260) (pH 7), 269.5 (ϵ 18170) (pH 2), 269.5 (ϵ 16700) (pH 11).

(−)-(2*R*,4*R*)-2-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]adenine (38). A solution of **36** (0.70 g, 1.37 mmol) in THF (30 mL) was treated with 1 M *n*-Bu_4NF–THF (1.64 mL, 1.64 mmol). After evaporation of the solvent, the crude product was crystallized from MeOH to give **38** (0.355 g, 95%) as white crystals: UV (H_2O) λ_{max} 264.0 nm (ϵ 14720) (pH 7), 264.0 (ϵ 14920) (pH 2), 263.8 (ϵ 15560) (pH 11).

(+)(2*R*,4*S*)-2-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]adenine (40). A solution of **39** (0.60 g, 1.17 mmol) in THF (30 mL) was treated with 1 M *n*-Bu_4NF/THF (1.4 mL, 1.4 mmol) to give **40** (0.27 g, 85%) as a white solid: UV (H_2O) λ_{max} 264.0 nm (ϵ 14640) (pH 7), 264.0 (ϵ 14880) (pH 2), 263.8 (ϵ 15030) (pH 11).

Antiviral and Cytotoxicity Assays. Antiviral studies with HIV-1 were performed in mitogen-stimulated human peripheral blood mononuclear (RBM) cells infected with strain LAV, as described previously.[20] A multiplicity of infection (MOI) of 0.1, as determined by a limiting dilution method in PBM cells, was selected for the assays. Stock solutions (40 mM) of the compounds were prepared in DMSO and then diluted in the medium to give the desired concentration. The maximal final concentration of DMSO in the solutions was less than 0.25%, which is not antiviral or cytotoxic to the cells. The compounds were added about 45 min after infection. The procedure for culturing the virus and the determination of supernatant RT levels has been described previously.[20] The drugs were also evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM, Vero, and CEM cells as described previously.[20] These cells were cultured with and without drug for 6, 3, and 6 days, respectively, at which time aliquots were counted in the presence of trypan blue.

Data Analysis. The medium effective concentration (EC_{50}) and inhibitory concentration (IC_{50}) values were derived from the computer-generated median effect plot of the dose-effect data, as described previously.[21]

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(14) (a) When the reaction mixture was stirred at −30 °C for 40 min, one anomeric mixture (N_3-isomer)[R_f = 0.41 (α) and 0.39 (β)-(hexanes–ethyl acetate, 1:1), UV λ_{max} 270.5 (MeOH), 263.5 (pH 2), 264.5 nm (pH 11)][14b] was almost exclusively formed. However, on stirring at room temperature for 1 h, the anomeric mixture was converted to another anomeric mixture of R_f value (N_9-isomer)[R_f = 0.78 (α) and 0.72 (β)(hexanes–ethyl acetate, 1:1), UV λ_{max} 264.5 nm (MeOH)] in the ratio of 1:1 (N_3/N_9-isomer) determined by isolated yield. Both anomeric mixtures were separately converted to amino derivatives by reacting with NH_3/MeOH in a steel bomb at 70 °C for 3 h, whose UV data (MeOH)(λ_{max}) were 271.0 nm and 259.5 nm, which were similar to those of N_3- and N_9-alkylated adenine,[14b-d] respectively. On the basis of the UV of 6-chloro and 6-amino derivatives, the isomer of lower R_f value was assigned to be N_3-isomer. However, repeating the completing reaction with N_3-isomers resulted in decomposition of the compounds instead of rearranging to N_9-isomer. (b) Prasad, R. N.; Robins, R. K. Potential Purine Antagonists. VIII. The Preparation of Some 7-Methylpurines. *J. Am. Chem. Soc.* **1957**, *79*, 6401–6407. (c) Leonard, N. J.; Deyrup, J. A. The Chemistry of Triacanthine. *J. Am. Chem. Soc.* **1961**, *84*, 2148–2160. (d) Robins, R. K.; Lin, H. H. Potential Purine Antagonists. IV. Synthesis of Some 9-Methyl-6-substituted-purines. *J. Am. Chem. Soc.* **1957**, *79*, 490–494.

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